

Serial No.: 10/806,899

### REMARKS

The Notice of Non-Compliant Amendment dated January 29, 2008 indicated that the Amendment dated December 21, 2007 was non-compliant because the listing of claims did not include the text of all pending claims. In particular, the Patent Office notes that the text for withdrawn claims 18, 19, 22 and 23 was not included. The Patent Office requires correction of the non-compliance.

Applicants have amended the listing of claims to include the text of withdrawn claims 18, 19, 22 and 23. Accordingly, applicants submit herewith an updated After-Final Amendment B with a revised "Amendments to the claims" section that includes the text of all pending claims.

Applicants therefore respectfully request withdrawal of the Non-Compliant status of After-Final Amendment B and further request that After-Final Amendment B be entered into the record and forwarded to the Examiner for consideration.

#### I. Status Summary

Claims 1-25 are pending in the subject application. Claims 18, 19, 22, and 23 have been withdrawn pursuant to a Restriction Requirement issued by the U.S. Patent and Trademark Office (hereinafter "the Patent Office"). Accordingly, claims 1-17, 20, 21, 24 and 25 have currently been examined and are pending in the Patent Office.

The Patent Office has dismissed applicants' claim for foreign priority, based on Australian Patent Application No. 2003/901425. As such, the Patent Office asserts that the instant claims do not have priority to the filing date of the Priority Document, and the effective filing date of the instant claims is the filing date of the instant application, or March 23, 2004.

Claims 1-17, 20, 21, 24 and 25 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Serial No.: 10/806,899

The Patent Office has rejected claims 1-17, 20, 21, 24 and 25 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 1-17, 20, 21, 24 and 25 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Patent Office has rejected claims 1-3, 5-10, 12, 16, 20, 24 and 25 under 35 U.S.C. §103(a) as allegedly being unpatentable over Claes et al. (2001) *Am J of Human Genet* 68:1327-1332 (hereinafter referred to as "Claes et al.").

The Patent Office has rejected claims 11, 13-15, and 17 under 35 U.S.C. §103(a) as allegedly being unpatentable over Claes et al. in view of U.S. Patent No. 6,331,614 to Wong et al. (hereinafter referred to as "Wong et al.").

Claims 1, 2, 4, 21, 24 and 25 have been amended herein. Support for the amended claims can be found throughout the specification as filed, including particularly at page 13 line 9, through page 14, line 2; and page 41, line 23-26. Further support can be found in Table 3 and in original claims 1 and 20. No new matter has been added.

Claims 3, 5-17 and 20 have been canceled. As such, claims 1, 2, 4, 21, 24 and 25 are currently pending in the instant application.

Reconsideration of the application based on the arguments set forth herein is respectfully requested.

## II. Response to the Objection to the Priority Claim

The Patent Office has acknowledged receipt of the certified copy of the priority application (Australian Patent Application No. 2003/901425; hereinafter the "Priority Document") upon which applicant has claimed foreign priority under 35 U.S.C. §119(b). However, the Patent Office asserts that adequate basis for the instant claims is not found in the Priority Document. As such, the Patent Office alleges that the instant claims do not have priority to the filing date of the Priority Document, and the effective

Serial No.: 10/806,899

filing date of the instant claims is the filing date of the instant application, or February 23, 2004. This rejection is respectfully traversed.

Initially the Patent Office asserts that claim 1 is not properly supported by the Priority Document because the element of testing for an alteration in a regulatory region is not disclosed in the Priority Document. In response, applicants respectfully submit that the Priority Document teaches the SCN1A gene is the most frequently mutated gene associated with SMEI. As such, the Priority Document discloses methods for testing a patient for SCN1A gene mutations in evaluating patients for SMEI. See, for example, page 5, lines 8-13 of the Priority Document. Applicants respectfully submit that "gene", as used in the context of the Priority Document disclosure, is believed to include both regulatory and non-regulatory regions. Therefore, applicants respectfully submit that claim 1 is believed to be adequately supported by the Priority Document.

The Patent Office also contends that claims 2 and 25 are not adequately supported by the Priority Document in that the Priority Document does not teach the element of establishing whether the alteration would result in a major disruption of the protein. In response applicants respectfully submit that the Priority Document discusses the nature of identified SCN1A gene alterations and their association with SMEI. For example, the Priority Document discloses that mutations in the  $\beta$ 1 subunit of SCN1B and alpha subunit of SCN1A result in critical changes to the proteins resulting in loss of function. See, for example, page 4, lines 6-20 of the Priority Document. Further, the Priority Document states that in identifying SCN1A gene alterations as they pertain to SMEI, known polymorphisms in the SCN1A gene should be accounted for as they are not associated with SMEI. See, for example, page 6, line 29, through page 7, line 4 of the Priority Document. As such, it is believed that one of skill in the art, upon review of the Priority Document disclosure, will understand that it is the SCN1A gene alterations that result in major disruptions (e.g. truncating alterations) to the SCN1A protein that result in SMEI. Therefore, applicants respectfully submit that claims 2 and 25 are believed to be adequately supported by the Priority Document.

Serial No.: 10/806,899

Support for claim 24 can be found at page 4, line 30, through page 5 line 7 and at page 14, lines 15-19, of the Priority Document. As such, claim 24 is believed to be adequately supported by the Priority Document.

Summarily, applicants respectfully submit that claims 1, 2, 24 and 25 are believed to be adequately supported by the Priority Document. As such, applicants respectfully submit that the priority claim to Australian Patent Application No. 2003/901425 under 35 U.S.C. §119(a)-(d) with respect to claims 1, 2, 24 and 25 is believed to be proper. Thus, applicants respectfully request that the instant objection to the priority claim regarding claims 1, 2, 24 and 25 be withdrawn at this time.

### III. Interview Summary

Applicants conducted a telephonic interview with Examiners Stephen Kapushoc and Ram Shukla on October 3, 2007. Participating in the telephonic interview with Examiners Kapushoc and Shukla were applicants' attorney of record, Arles A. Taylor, Jr. and patent agent Leon R. Legleiter. Applicants sincerely appreciate the Examiners' time and consideration in agreeing to and participating in the telephonic interview.

During the telephonic interview the overall concept of the disclosed and claimed subject matter was discussed. Applicants and Examiners Kapushoc and Shukla reached an agreement that the disclosed method is directed to a method of categorizing or classifying patients as likely or unlikely to have SMEI. As such, it was agreed that the when viewed as a method of categorizing patients the claims were adequately enabled by the specification. The prior art was also discussed along with potential options for distinguishing the presently disclosed subject matter. Applicants respectfully submit that the Amendments and Remarks presented herein are believed to be consistent with their understanding of the Examiners' position as presented during the telephonic interview.

Serial No.: 10/806,899

IV. Response to the 35 U.S.C. §112, Second Paragraph, Rejection of  
Claims 1-17, 20, 21, 24 and 25

Claims 1-17, 20, 21, 24 and 25 have been rejected under 35 U.S.C. §112, second paragraph, on several bases as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Initially, applicants respectfully submit that claims 3, 5-17 and 20 have been canceled herein, therefore mooted the instant rejections with respect to these claims.

The Patent Office asserts that claims 1-3, 5-17, 20, 24, and 25 are unclear over the recitation of the phrase 'testing a patient sample for the existence of an alteration in the SCN1A gene', as recited in claim 1. Particularly, the Patent Office asserts it is unclear what applicant intends for the phrase to encompass and thus the metes and bounds of the claimed subject matter are not clearly defined.

With respect to independent claim 1 and claims depending therefrom, applicants respectfully submit that claim 1 has been amended herein to recite a method for determining the likelihood that a patient suspected of SMEI does or does not have SMEI, comprising, *inter alia*, screening a patient sample for the existence of an alteration in the SCN1A gene of a patient, including in a regulatory region of the gene, by sequencing the SCN1A gene. Claim 21 has also been amended in a similar manner. Support for the amendments to claims 1 and 21 can be found throughout the specification as filed, including particularly at page 13, line 9, through page 14, line 2; page 4, line 23-26; and in claim 20. No new matter has been added.

As such, after a review of the subject patent application, one of ordinary skill in the art at the time the application was filed would be able to ascertain the metes and bounds of the subject matter of "screening a patient sample for the existence of an alteration in the SCN1A gene...by sequencing the SCN1A gene."

In response to the Patent Office's assertions that it is unclear to what the alteration is being compared, applicants particularly point to page 13, lines 11-14, which recites:

Serial No.: 10/806,899

Comparison of the SCN1A DNA wild-type sequence with the SCN1A sequence of a test patient provides both high specificity and high sensitivity.

Accordingly, applicants respectfully submit that upon review of the present disclosure, one of ordinary skill in the art would understand that an alteration in the SCN1A gene can be determined based upon a comparison to the wild-type SCN1A gene.

Further, applicants respectfully submit that one of skill in the art would understand, based upon a review of the instant disclosure, that the longer SCN1A wild-type isoform, as indicated in the footnotes at the bottom of Table 3, can be used in determining the presence of an alteration in the SCN1A gene. In addition, applicants respectfully submit that at the time of the invention the SCN1A wild-type sequence was known to those of ordinary skill in the art. See, for example, post-filing publications to Mulley et al. (2005, *Human Mutation*, 25:535-542) and Harkin et al. (2007, *Brain*, 130:843-852), both of which refer to the "longer isoform" or "full-length" isoform of the SCN1A gene as the reference or wild-type sequence, also designated as GenBank accession number AB093548.

Additionally, applicants respectfully submit that for each of the SCN1A alterations listed in Table 3, a corresponding SEQ ID NO. is also included. Each of these sequences referred to in Table 3 contains only one alteration. As such, one of skill in the art would understand that reversing the single alteration provides the reference or wild-type sequence. Using the *c251A*→*G* mutation as an example, one of skill in the art would recognize that the reference or wild-type sequence can easily be generated by changing the G back to an A at coding position 251 of SEQ ID NO: 1.

Accordingly, applicants respectfully submit that the metes and bounds of the phrase "screening a patient sample for the existence of an alteration in the SCN1A gene...by sequencing the SCN1A gene" has been sufficiently defined in the instant specification, so as to encompass all forms of gene mutations, including deletions, insertions, rearrangements and point mutations compared to the wild-type SCN1A

Serial No.: 10/806,899

gene. Such a comparison is believed to be within the knowledge of one of ordinary skill in the art and sufficiently disclosed in the specification. Thus, applicants respectfully submit that the instant rejection has been addressed.

Additionally, the Patent Office asserts that claims 1-17, 20, 24 and 25 are unclear in view of the recitation of the phrase "known to be". Particularly, the Patent Office asserts that it is unclear what is required for any particular mutation to be "known to be SMEI associated".

In response, applicants respectfully submit that after reviewing the specification, one of ordinary skill in the art at the time the application was filed would understand that when a particular mutation is "known to be SMEI associated", the mutation has been previously determined to be associated with SMEI.

However, in an effort to further prosecution and without acquiescing to the contentions of the Patent Office, applicants respectfully submit that claim 1 has been amended by omitting the phrase "known to be" and adding language to clarify the presently claimed subject matter. In particular, claim 1 has been amended to recite, *inter alia*, ascertaining whether the alteration, when one is detected, has previously been detected in a patient clinically diagnosed with SMEI and is therefore considered SMEI associated or has previously been detected in a patient not diagnosed with SMEI and is therefore considered non-SMEI associated or is not considered to be either; wherein (a) the patient is categorized as having a high probability of having SMEI when the alteration is SMEI associated; (b) the patient is categorized as having a low probability of having SMEI when the alteration is non-SMEI associated; or (c) further analysis is undertaken to establish the likelihood the patient suspected of SMEI does or does not have SMEI when the detected alteration is not considered to be either SMEI associated or non-SMEI associated. Support for these amendments can be found throughout the specification as filed and particularly at page 5, lines 1-25; page 14, lines 29-32; Figure 1; and Table 3.

Thus, applicants respectfully submit that the instant rejection of claim 1 has been addressed.

Serial No.: 10/806,899

The Patent Office further asserts that claims 2 and 25 are unclear in view of the recitation of the phrase "a major disruption to the protein." Specifically, the Patent Office asserts that it is unclear what is included within "a major disruption".

In response, applicants respectfully submit that after reviewing the specification, one of ordinary skill in the art at the time the application was filed would understand what is intended by the phrase "a major disruption of the protein". Particularly, applicants respectfully submit that one of ordinary skill in the art would understand that a major disruption in a protein could include any alteration in the SCN1A gene that can cause a change in the protein conformation and/or function. For example, a major disruption in a protein can include truncating alterations, missense mutation, and so forth.

However, in an effort to further prosecution and without acquiescing to the contentions of the Patent Office, applicants respectfully submit that claims 2 and 25 have been amended by replacing the phrase "a major disruption to a protein" with the phrase "a truncating alteration to a protein". Support for the amendments to claims 2 and 25 can be found throughout the specification as filed, and particularly at page 42, lines 2-8.

Thus, applicants respectfully submit that the instant rejections of claims 2 and 25 have been addressed.

The Patent Office asserts that claim 4 is unclear over the recitation of the phrase "wherein the alteration is one identified in Table 3" in view of the species election of the c251A→G nucleotide change.

In response, applicants respectfully submit that the Patent Office appears to be requiring applicants to limit the subject matter of claim 4 to the c251A→G nucleotide change.

Applicants respectfully submit that claim 4 has been amended to recite [a] method as claimed in claim 1 wherein the alteration is one of the nucleotide changes identified in Table 3 as SMEI associated or non-SMEI associated. Support for this



Serial No.: 10/806,899

amendment can be found throughout the specification as filed and particularly in Table 3.

Thus, applicants respectfully submit that the instant rejection of claim 4 has been addressed.

The Patent Office asserts that claim 21 is unclear over the recitation of the phrase "alteration as laid out in Table 3" in view of the species election of the c251A→G nucleotide change.

In response, applicants respectfully submit that the Patent Office appears to be requiring applicants to limit the subject matter of claim 21 to the c251A→G nucleotide change.

Applicants respectfully submit that claim 21 has been amended to recite, *inter alia*, ascertaining whether the alteration, when one is detected, is as laid out in column 3 of Table 3. Support for this amendment can be found throughout the specification as filed and particularly in Table 3.

Thus, applicants respectfully submit that the instant rejection of claim 21 has been addressed.

The Patent Office also asserts that claim 21 is unclear over the recitation of the phrase "known to be" in reference to whether a detected alteration is SMEI associated or non-SMEI associated. This rejection is believed to be addressed with the amendments discussed herein above with respect to claim 1.

Finally, the Patent Office asserts that the preamble of claims 1 and 21 indicates a method for the diagnosis of SMEI in a patient, but that there is no final step in which SMEI is actually diagnosed in the patient.

Without acquiescing to the contentions of the Patent Office and in an effort to further prosecution, applicants respectfully submit that claims 1 and 21 have been amended herein. In particular, claims 1 and 21 have been amended to recite, *inter alia*, wherein the detection of a SMEI associated alteration establishes that a patient suspected of SMEI likely does have SMEI.

Serial No.: 10/806,899

Thus, applicants respectfully submit that the instant rejection of claim 21 has been addressed.

In summary, applicants respectfully submit that each rejection of claims 1, 2, 4, 21, 24 and 25 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite has been addressed. Accordingly, applicants respectfully request that the instant rejection of claims 1, 2, 4, 21, 24 and 25 be withdrawn at this time. Allowance of the claims is also respectfully requested.

V. Response to the 35 U.S.C. §112, First Paragraph, Written Description Rejection of Claims 1-17, 20, 21, 24, and 25

The Patent Office has rejected claims 1-17, 20, 21, 24, and 25 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Particularly, the Patent Office asserts that an adequate written description is not provided for the broadly claimed methods encompassing the detection of any alteration in the SCN1A gene in a patient and making a diagnosis by detecting the alteration.

The Patent Office further asserts that the claims encompass ascertaining whether the alteration is known to be SMEI-associated or non-SMEI-associated, without sufficient teaching in the specification of the detection and analysis of nucleic acid sequences comprising SCN1A alterations of such a large genus as encompassed by the claims.

Further, the Patent Office asserts that the specification does not adequately teach one of ordinary skill in the art how to identify an SCN1A mutation that is "known to be SMEI-associated" or "non-SMEI-associated."

After careful consideration of the rejections and the Patent Office's basis therefore, applicants respectfully traverse the rejections and submit the following remarks.

Preliminarily, applicants respectfully submit that claims 3, 5-17 and 20 have been canceled herein, therefore mooted the instant rejections with respect to these claims.

Serial No.: 10/806,899

Initially, applicants note that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). Thus, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Patent Office to rebut the presumption. See Manual of Patent Examining Procedure (hereinafter "MPEP") § 2163.04 citing In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Further, as a matter of Patent Office practice, the burden rests upon the Patent Office to establish a *prima facie* case of a failure to comply with 35 U.S.C. §112, first paragraph, with respect to the invention described and claimed in applicants' patent application. See Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement (hereinafter "The Guidelines"), 66 Fed. Reg. at 1105. This includes "the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims". Id. The Patent Office must establish "by a preponderance of the evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined in the claims". Id. at 1107, citing Wertheim, at page 263. The Patent Office, therefore, must have a reasonable basis to challenge the adequacy of the written description, and, in rejecting a claim, the Patent Office must set forth express findings of fact which support the lack of written description rejection.

Additionally, applicants note that there is "an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement". Id. at 1105, citing Hybridtech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). With regard to the "representative number of species" necessary to describe an entire genus, applicants further note that what constitutes such a representative number is also an inverse function of the skill and knowledge in the art. Satisfactory disclosure is achieved if the skilled artisan recognizes from the disclosed species that the applicant

Serial No.: 10/806,899

was "in possession of the necessary common attributes or features of the elements possessed by the genus" *Id.* at 1106.

Applicants respectfully submit that claims 1 and 21 have been amended herein. In particular, claim 1 now recites, [a] method for determining the likelihood that a human patient suspected of SMEI does or does not have SMEI comprising: *inter alia*, screening a patient sample for the existence of an alteration in the SCN1A gene of the patient, including in a regulatory region of the gene, by sequencing the SCN1A gene; and ascertaining whether the alteration, when one is detected, has previously been detected in a patient clinically diagnosed with SMEI and is therefore considered SMEI associated or has previously been detected in a patient not diagnosed with SMEI and is therefore considered non-SMEI associated or is not considered to be either. Claim 21 has been amended in a similar manner.

Support for the amended claims can be found throughout the specification as filed, including particularly at page 13 line 9, through page 14, line 2; page 41, line 23-26. Further support can be found in Table 3 and in original claims 1 and 20. No new matter has been added.

Accordingly, applicants respectfully submit that the specification of the subject application teaches methods that would allow one of ordinary skill in the art to screen for an alteration in the SCN1A gene, as claimed. Further, applicants respectfully submit that upon review of the present disclosure, one of ordinary skill in the art would readily be able to ascertain whether a detected alteration has previously been detected in a patient clinically diagnosed with SMEI and is therefore considered SMEI associated or has previously been detected in a patient not diagnosed with SMEI and is therefore considered non-SMEI associated or is not known considered to be either. As such, one of skill in the art, upon review of the instant disclosure, will be able to categorized a patient based upon their probability of having SMEI.

Thus, applicants respectfully submit that the specification of the subject application as filed fully discloses the subject matter encompassed by the presently amended claims. Therefore, applicants submit that claims 1, 2, 4, 21, 24 and 25 comply

Serial No.: 10/806,899

with the written description requirement of 35 U.S.C. §112, first paragraph. Thus, applicants respectfully submit that the instant 35 U.S.C. §112, first paragraph, rejection of claims 1, 2, 4, 21, 24 and 25 as allegedly failing to comply with the written description requirement has been addressed. Accordingly, applicants respectfully request that the instant rejection be withdrawn at this time. Allowance of claims 1, 2, 4, 21, 24 and 25 is also respectfully requested.

VI. Response to the 35 U.S.C. §112, First Paragraph, Enablement Rejection of Claims 1-17, 20, 21, 24 and 25

Claims 1-17, 20, 21, 24 and 25 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

After careful consideration of the rejection and the Patent Office's basis therefore, applicants respectfully traverse the rejection and submit the following remarks.

Preliminarily, applicants respectfully submit that claims 3, 5-17 and 20 have been canceled herein, therefore mooted the instant rejections with respect to these claims.

Applicants initially submit that as a matter of Patent Office practice, the burden rests upon the Examiner to establish a *prima facie* case of a failure to comply with 35 U.S.C. §112, first paragraph, with respect to the subject matter described and claimed in Applicants' patent application. See In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). Applicants respectfully submit that the Examiner has not met the burden of establishing a *prima facie* case of a failure to comply with 35 U.S.C. §112, first paragraph, and traverse the Examiner's rejection of claims 1-17, 20, and 21 under 35 U.S.C. § 112, first paragraph, as follows.

Applicants further submit that the appropriate standard for measuring enablement under 35 U.S.C. §112, first paragraph, is that the claimed subject matter must be enabled so that a person skilled in the art can make and use the invention from

Serial No.: 10/806,899

the disclosures of the specification, coupled with information known in the art, without "undue experimentation." In re Wands, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). Further, the quantity of experimentation to be performed by one of ordinary skill in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the U.S. patent application in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed." In re Wands, 8 U.S.P.Q.2d at 1404 (citing In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. U.S. v. Teletronics, Inc., 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989). Specific comments presented by the Examiner in view of the appropriate standard for measuring enablement under 35 U.S.C. §112, first paragraph, are addressed as follows.

Initially, the Patent Office asserts that the claims are drawn to methods for the diagnosis of SMEI in a patient, and encompass any subject organism including non-human subjects. Accordingly, the Patent Office asserts that the claims require knowledge of whether or not any particular detected mutation is known to be SMEI associated or non-SMEI associated, and further depends on the concept that any detected *de novo* mutation in the SCN1A gene is indicative of SMEI.

In response, applicants respectfully submit that claims 1 and 21 have been amended as discussed hereinabove. First, claims 1 and 21 have been amended to now recite a "human" patient. Further, applicants respectfully submit that amended claim 1 is drawn to a method of determining the likelihood that a patient has SMEI by screening for alterations in the SCN1A gene by sequencing the gene and if an alteration is detected, ascertaining whether the alteration has previously been associated with SMEI so as to provide the ability to categorize the patient based upon the likelihood that they

Serial No.: 10/806,899

indeed have SMEI. Claim 21 has been amended in a similar matter, but is directed to the mutations as laid out in column 3 of Table 3.

As such, the instant claimed methods are not directed to a method of diagnosing SMEI, but rather a method of categorizing patients based upon the likelihood that they have SMEI. To elaborate, a conventional diagnostic test involves an analysis of a piece of DNA to establish whether or not a mutation exists, *i.e.*, if the mutation is present the diagnosis will be positive for the disease state, and if the mutation is absent the diagnosis will be negative for the disease state, depending on the nature of the disease. Generally, the test involves amplification of one single and specific portion of a gene to establish whether or not the mutation is present.

However, as disclosed in the subject application, a "patient down" perspective allows the identification of specific mutations that are causative of certain disease states. Further, SMEI does not have one single cause, hence a diagnostic test that seeks to establish the presence or absence of a mutation identified in a study based on a small group of patients would at best identify the disease only a small proportion of the patients. Further, mutations in SCN1A can be linked with other diseases, and thus these mutations are not causative or indicative of SMEI. Accordingly, as set forth in the subject application, a conclusion cannot definitively be drawn that SMEI is always associated with a mutation in SCN1A, or that all mutations in SCN1A result in SMEI.

In view of these difficulties, a conventional diagnostic test wherein a portion of the SCN1A gene is amplified to establish the presence or absence of a particular mutation cannot be established. Rather, the presently claimed subject matter looks at the totality of the genetic landscape for SCN1A.

In the first leg of the approach, SCN1A is screened, a mutation that has been previously detected in a patient clinically diagnosed with SMEI is discovered, and a likelihood of high probability of SMEI is determined. In the second leg of the approach, SMEI is screened, a mutation that has previously been identified in a patient not diagnosed with SMEI and is therefore not associated with SMEI is identified, and a likelihood of low probability of SMEI is determined. In the case where the mutation

Serial No.: 10/806,899

proves to be neither SMEI associated nor non-SMEI associated, the likelihood of high/low probability of SMEI is not determined immediately, but is investigated further. In some embodiments, the specification of the subject application sets forth that after establishing whether or not the mutation has arisen *de novo* and/or whether it is a truncating mutation, the likelihood of SMEI can be set out as in Figure 1.

Accordingly, the first leg of the test can define nothing more than a conventional test if one were actually testing for a known mutation. However, this is not what occurs, because identification of a known mutation is just one possible result of the SCN1A screen. Unlike a conventional diagnostic test, in the disclosed methods, the SCN1A gene is screened for the presence of any mutation (as compared to a single and specific mutation expected in a conventional diagnostic test), and how the test proceeds depends on whether the mutation falls into the first, second, or third leg of the test.

In addition, as set forth in the specification of the subject application, the test can involve DNA sequencing to enable identification of characterization of a mutation anywhere in the gene. In comparison, a conventional diagnostic test seeking to identify a specific mutation associated with a disease state will generally involve amplification of a specific sequence within the gene, often with only the desired form of the gene being amplified. If the result is negative, a negative diagnosis is entered and if the result is positive, a positive diagnosis is entered.

In comparison, in the presently claimed subject matter, there is no test for the presence or absence of any specific mutation. Applicants further submit that a great number of mutations associated with SMEI occur in the SCN1A gene, and thus the disclosed methods can be used as an aid in the determination of the likelihood of SMEI.

Accordingly, it is apparent from a review of the instant specification that aspects of the presently disclosed and claimed subject matter lie in the identification of three possible categories of results upon initial screening of a patient suspected of having SMEI, and provision of steps involved in determining the likelihood of SMEI.



Serial No.: 10/806,899

Therefore, applicants respectfully submit that the presently claimed subject matter provides a method to be employed to make a determination of the likelihood of SMEI in circumstances where screening can identify mutations previously detected in patients with SMEI, mutations previously detected in patients not diagnosed with SMEI, and mutations that have not previously been associated with either. Clearly, any and all mutations in the SCN1A subunit will fall into one of these three categories. Accordingly, a complete method for the determination of the likelihood of SMEI is disclosed and enabled, irrespective of whether the mutation has previously been detected in patients with SMEI.

Accordingly, applicants respectfully submit that the instant 35 U.S.C. §112, first paragraph, enablement rejection of claims 1, 2, 4, 21, 24 and 25 has been addressed. Thus, applicants respectfully request that the instant rejection be withdrawn at this time. Allowance of claims 1, 2, 4, 21, 24 and 25 is also respectfully requested.

VII. Response to the 35 U.S.C. §103(a) Rejection of Claims 1-3, 5-10, 12, 16, 20, 24 and 25 in view of Claes *et al.*

The Patent Office has rejected claims 1-3, 5-10, 12, 16, 20, 24 and 25 under 35 U.S.C. §103(a) upon the contention that the claims are unpatentable over Claes *et al.* Particularly, the Patent Office asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the explicit teachings of Claes *et al.* to perform an analysis of a patient suspected of SMEI that meets all of the required limitations of the rejected claims.

After careful consideration of the rejection and the Patent Office's basis therefore, applicants respectfully traverse the rejection and submit the following remarks.

Preliminarily, applicants respectfully submit that claims 3, 5-17 and 20 have been canceled herein, therefore mooted the instant rejections with respect to these claims.

Initially, applicants respectfully submit that in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some

Serial No.: 10/806,899

suggestion or motivation in the references themselves to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. Manual of Patent Examining Procedures (M.P.E.P.) 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Furthermore, even when the combination of references teaches every element of the claimed invention, without a motivation to combine a rejection based on a *prima facie* case of obviousness is improper. *In re Rouffet*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). Further, "the level of skill in the art cannot be relied upon to provide the suggestion to combine references". MPEP § 2143.01, citing *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). As such, under these criteria applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness under 35 U.S.C. §103(a) with respect to claims 1-4, 21, 24 and 25 over the cited reference(s).

Assuming *arguendo* that the Patent Office has satisfied its burden of presenting a *prima facie* case of obviousness, applicants respectfully submit the following.

It is believed that Claes et al. does not teach or suggest the methodology of the present claims. At best, the fact that 7 separate mutations are identified and all are associated with SMEI also, with hindsight, starts to lead to the realization that a conventional test was not possible. However it is believed to be counterintuitive to consider this impossible situation with multiple causes of a disease, and then decide to screen the whole gene for mutations and categorise them as "SMEI associated", "non-SMEI associated" and "neither SMEI associated nor non-SMEI associated" and then to further investigate the last category, not as a scientific study, but for each diagnosis with the results going back to the clinician each time for each patient. Claes et al. does not suggest that (a) there are many more de novo mutations associated with SMEI; (b) some mutations in SCN1A not associated with SMEI; and (c) it does not suggest that

Serial No.: 10/806,899

analysis undertaken to establish these points for other, previously uncharacterised mutations could be strongly suggestive that these mutations too cause SMEI.

Applicants respectfully disagree with the Patent Office's contention at page 30 of the outstanding official action that "a method in which a particular mutation is identified and used to diagnose SMEI will satisfy the limitations of the claimed method". If one is looking for a particular mutation, as a matter of practicality, primers would be prepared to amplify the portion of the gene that contains the mutation. But, present claims 1 and 21 recite sequencing of the gene. See also instant Examples 2 and 3, in which all of the exons were amplified and sequenced.

Accordingly, applicants respectfully submit that independent claims 1 and 21 are directed to a "gene up" approach for determining the likelihood that a patient has SMEI. To elaborate, the presently claimed subject matter is directed to whether SMEI can be screened by looking at the totality of the genetic landscape for the SCN1A gene coding the alpha 1 subunit of the sodium channel. Particularly, the "gene up" approach as recited in independent claims 1 and 21 comprises a first leg wherein once the SCN1A gene in a patient is screened, a categorization of high likelihood of SMEI is entered if a mutation that has been previously identified with SMEI is discovered. In the second leg, a characterization of a low probability of SMEI is entered if the mutation in the SCN1A gene has been previously identified as one not associated with SMEI. In the case where the mutation is neither SMEI associated nor non-SMEI associated, a characterization is not immediately entered, but is investigated further.

Hence, applicants respectfully submit that the instant 35 U.S.C. §103(a) rejection of claims 1, 2, 24 and 25 as allegedly being unpatentable over Claes et al. has been addressed. Accordingly, applicants respectfully request that the rejection of claims 1, 2, 24 and 25 be withdrawn at this time. A Notice of Allowance directed to these claims is also respectfully requested.

Serial No.: 10/806,899

VIII. Response to the 35 U.S.C. §103(a) Rejection of Claims 11, 13-15, and 17  
Over Claes et al. in view of Wong et al.

The Patent Office has rejected claims 11, 13-15, and 17 under 35 U.S.C. §103(a) as allegedly being unpatentable over Claes et al. in view of Wong et al. Particularly, the Patent Office asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the combined teachings of Claes et al. and Wong et al. to perform an analysis of a patient suspected of SMEI that meets all of the required limitations of the rejected claims.

In response, applicants respectfully submit that without acquiescing to the contentions of the Patent Office and in an effort to further prosecution the instant rejected claims have been canceled. As such, applicants respectfully submit that the instant rejection is mooted and respectfully request that the rejection of claims 11, 13-15, and 17 under 35 U.S.C. § 103(a) be withdrawn at this time

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Serial No.: 10/806,899

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any other fees associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,

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